REMARKS

The Examiner is invited to telephone the undersigned to discuss any issues deemed remaining after consideration of this amendment.

A Petition for a two-month extension of time is submitted herewith. The Petition authorizes a charge to our Deposit Account No. 19-0365 for the fees for this extension. The grant of this extension makes March 5, 2005 the due date for response instead of January 5, 2005. Since March 5, 2005 was a Saturday, the due date for response becomes March 7, 2005.

The Claims have been amended to expedite prosecution and to better define Applicants' claimed invention.

Applicants reserve the right to pursue the deleted subject matter in an appropriately filed continuing application.

Claims 1, 2, 8-10, 14-16, 19-21, 24 and 25 have been amended. Support for the amendments may be found, for example, in the claims as originally filed, and on page 4 at lines 20 to 26.

Claim 1 incorporates the limitations of Claims 4, 6, 7 and 12.

Claim 3 is as originally filed.

Claims 4-7, 11-13, 17, 18, 22 and 23 have been cancelled without prejudice.

Claims 1-3, 8-10, 14-16, 19-21, 24 and 25 remain in the application.

Objection

The objection to Claim 24 is deemed obviated by the amendment to the Claim.

The Examiner is requested to reconsider and to withdraw this objection.

Rejection under 35 U.S.C. 112, 2nd paragraph

Claims 1 to 25 stand rejected under 35 U.S.C. 112, 2nd paragraph for the reasons of record.

Applicants' specification does conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicants regard as the invention.

However, in order to expedite prosecution the claims have been amended to obviate this rejection.

Claims 15 and 24 now depend on Claim 3. Claim 3 depends on Claim 2. Claim 2 depends on Claim 1. The antecedent basis is provided by the chain of claim dependency.

The Examiner is therefore requested to reconsider and withdraw this rejection.

Rejection under 35 U.S.C. 102(b)

Claim 1 stands rejected under 35 U.S.C. 102(b) as being anticipated by Hudziak et al. (U.S. 5,770,195) or Schwall et al. (U.S. 5,686,292).

Hudziak et al. disclose a method of inhibiting growth of tumor cells by treatment with antibodies that inhibit the growth receptor function (e.g., HER2 receptor function).

Hudziak et al. also disclose the administration of antibodies capable of inhibiting growth factor receptor function and a cytotoxic factor. Amongst the cytotoxic factors there is disclosed chemotherapeutic drugs. Among the chemotherapeutic drugs there is disclosed doxorubicin. See Col. 6 at about lines 60-65, and Claims 14, 23 and 24 in Column 20.

Schwall et al. disclose Hepatocyte growth factor (HGF) receptor antagonists. Schwall, et al. also disclose methods of treating cancer using the HGF receptor antagonists.

Schwall et al. also disclose that the antagonists may also be administered in combination with one or more other therapeutic agents. Amongst the therapeutic agents there is listed chemotherapeutic agents. Amongst the chemotherapeutic agents there is listed Doxorubicin and Cyclophosphamide (see Col. 13 at about lines 38-54).

Neither Hudziak et al. or Schwall et al. disclose a method of treating cancer using a pegylated liposomal doxorubicin as required by Applicants' claimed invention.

Neither Hudziak et al. or Schwall et al. disclose Applicants' presently claimed specific combination of pegylated liposomal doxorubicin and Trastuzumab (e.g., Herceptin) for the treatment of cancer.

Neither Hudziak et al. or Schwall et al. disclose Applicants' presently claimed specific combination of pegylated liposomal doxorubicin, Trastuzumab and additional additional antineoplastic agent (e.g., Cyclophosphamide).

Therefore, neither Hudziak et al. or Schwall et al. anticipate Applicants' presently claimed invention.

The Examiner is therefore requested to reconsider and withdraw this rejection.

Rejected under 35 U.S.C. 102(e)

Claim 1 stands rejected under 35 U.S.C. 102(e) as being anticipated by Cohen et al. (WO 02/053596, priority to January 5, 2001) for the reasons of record.

Cohen et al. disclose IGF-IR antibodies and their combination with, for example Adriamycin (doxorubicin), or with the EGF-R tyrosine kinase inhibitor CP-358,774 (see page 7 at liens 1, 2, 9, 10 and 13 to 15).

Cohen et al. also disclose that the anti-IGF-IR can be coformulated with and/or coadministered with one or more additional therapeutic agents, such as a chemotherapeutic agent, an antineoplastic agent or an anti-tumor agents (see p. 59 at lines 1 to 19).

Cohen et al. also disclose that a compound of their invention can be used with signal transduction inhibitor, such as, for example erbB2 receptor inhibitors, such as for example Herceptin (see p. 63 at lines 3 to 9). See also the disclosure about combination with ErbB2 receptor inhibitors on page 64 at lines 14 to 30.

Cohen et al. also disclose therapeutic methods of use on pages 68 to 70 for example. They also disclose co-administration of the anti-IGF-IR antibody with other therapeutic agents on page 71.

However, Cohen et al. do not disclose Applicants' presently claimed methods requiring the use of pegylated liposomal doxorubicin and Trastuzumab (Herceptin), or requiring the use of pegylated liposomal doxorubicin, Trastuzumab and another antineoplastic agent (e.g., cyclophosphamide).

Cohen, et al.'s disclosure on page 57 (lines 25-27) that their composition can be formulated as a liposome is not a disclosure of Applicants' methods of treatment using a pegylated liposome doxorubicin.

Thus, Cohen et al. do not anticipate Applicants' presently claimed invention.

The Examiner is therefore requested to reconsider and withdraw this objection.

Rejection under 35 U.S.C. 102(e)

Claims 1, 2, 4, 6, 12 and 18 stand rejected under 35 U.S.C. 102(e) as being anticipated by Waksal, et al. (U.S. 2002/0012663) as evidenced by Mendelsohn, et al. (U.S. 4,943,533) and Physicians Desk Reference On-Line Edition (PDR) 2004, for the reasons of record.

Waksal et al. disclose a method of inhibiting the growth of refractory tumors that are stimulated by a ligand of epidermal growth factor receptor (EGFR). The method comprises treatment with an EGFR/HER1 antagonist.

Waksal et al. disclose that the EGFR/HER1 antagonists include biological molecules. The biological molecules include derivatives of any of these molecules. For example, derivatives of biological molecules include lipid and glycosylation derivatives of oligopeptides, polypeptides, peptides and proteins (see paragraphs 0037 and 0038).

Waksal et al. disclose treatment with an EGFR/HER1 antagonist and chemotherapeutic agents (see page 6, paragraph 0083). Paragraph 0087 on page 6 discloses preferred chemotherapeutic agents including cyclophosphamide and doxorubicin (Adriamycin).

Waksal, et al. do not disclose Applicants' claimed methods requiring the use of pegylated liposomal doxorubicin. Therefore, Applicants' presently claimed methods are not disclosed.

Therefore, Waksal, et al. do not anticipate Applicants presently claimed invention.

The Examiner is requested to reconsider and withdraw this rejection.

35 U.S.C. 103(a) Rejections

Applicants wish to direct the Examiner's attention to the abstract in the Am Soc Clin Oncol, vol 23, page 34, abstract number 630, 2004 (Chia et al.) submitted herewith to illustrate the unobviousness of Applicants' claimed invention. The abstract is directed to a multi-centre phase II trial of pegylated liposomal doxorubicin and trastuzumab in HER-2 over-expressing metastatic breast cancer (MBC). The abstract discloses that although combination therapy with conventional doxorubicin and trastuzumab improves clinical outcome in HER-2 + MBC, a 27% cardiac dysfunction prevents clinical use of this combination. The abstract discloses that in a large phase III trial in MBC, pegylated liposomal doxorubicin (Caelyx) was equally efficacious as conventional doxorubicin, but with significantly less cardiotoxicity. The abstract discloses that the combination of Caelyx and trastuzumab are synergistic in multiple breast cancer cell lines. Of 30 patients enrolled in the study 3 patients (i.e. 10%) experienced protocol-defined cardiotoxicity compared to the above mentioned 27% cardiac dysfunction with conventional doxorubicin and trastuzumab.

In view of this information, and the remarks addressed to the 35 U.S.C. 103(a) rejections below, Applicants believe their claimed invention patentably distinguishes over the cited references.

Rejection under 35 U.S.C. 103(a)

Claims 1, 2, 4, 6, 8, 9, 10, 12, 18 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Waksal et al. in view of Kastrup et al. and Parahahadiopoulos et al.

The reference alone or combined do not teach, disclose or suggest Applicants' claimed invention.

Waksal et al. have already been discussed above and the remarks apply equally, as well as here.

Kastrup et al. dicsuss Doxorubicin HCl.

Parahahadiopoulos et al. disclose findings obtained with liposomes sterically stabilized by the PEG head groups of a synthetic phospholipid (PEG-DSPE) included in the formulation (PEG-liposomes).

In the second paragraph of the first column on page 11461. Papahadjopoulos, et al. discloses that liposomes containing doxorubicin (or epirubicin) were composed of PEG-DSPE/HSPC/chol/α-toxopherol.

Parahadjopoulos et al. disclose an experimental model of lymphoma grown i.p. with an i.v. injection of PEG-DSPE/HSPC/chol liposomes encapsulating doxorubicin (col. 2, page 11462). The authors disclose that the results indicate that encapsulation in PEG-liposomes diminished the early uptake of the drug by the heart and liver (see third sentence, left column, page 11463).

Parahadjopoulos et al. disclose the results of a study with mouse colon carcinoma grown s.c. For the therapeutic experiments, multiple injections of liposomes composed of PEG-DSPE/HSPC/chol loaded with epirubicin were given. The authors disclose that encapsulation causes marked improvement in therapeutic efficacy, inhibiting the tumor growth and producing a large percentage of long-term survivors (see first column page 11463). The authors also disclose that they can conclude that the acute toxicity of epirubicin, as exemplified by the maximum tolerated dose, is reduced slightly following liposome encapsulation (see col. 2, p. 11463).

Parahadjopoulos et al. also disclose (Col. 1, p. 11464) that their therapeutic studies with PEG-DSPE/HSPC/chol liposomes showed a significant increase in the therapeutic index of antitumor drugs in mice against both a lymphoma and a colon carcinoma. The authors also disclose that the lower acute toxicity of anthracycline-loaded PEG-liposomes reported here is similar to that observed earlier with conventional liposomes.

However, the cited references do not teach, disclose or suggest methods of treatment using the pegylated liposome doxorubicin and Trastuzumab (Herceptin), or

using the pegylated liposome doxorubicin, Trastuzumab and another antineoplastic agent (e.g., cyclophosphamide), as claimed by Applicants.

Applicants claimed invention is deemed to patentably distinguish over the cited references.

The Examiner is therefore requested to reconsider and withdraw this rejection.

Rejection under 35 U.S.C. 103(a)

Claims 1-9 and 11-24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Albanell and Baselga in view of Kastrup et al. and Parahadadiopoulos et al. for the reasons of record.

Albanell et al. disclose that data from phase II trials in woman with breast cancer whose tumors overexpress HER2 have shown that trastuzumab has a favorable toxicity profile, is active as a single agent and induces long-lasting objective tumor responses (see Col. 2 page 931).

Albanell et al. disclose that paclitaxel and doxorubicin have been shown to be the most active chemotherapeutic agents for the treatment of patients with breast cancer. Albanell et al. further state that it was hypothesized that the antitumor activity of these drugs could be enhanced by combining them with anti-HER2 MAba. Thus, Albanell et al. conducted a series of experiments with trastuzumab in combination with paclitaxel or doxorubicin (see Col. 2, second paragraph).

Albanell et al. disclose the design of a phase III multicenter clinical trial of chemotherapy (doxorubicin- or paclitaxel-based) plus trastuzumab versus chemotherapy alone in patients with advanced breast cancer overexpressing HER2. The authors discuss the results of doxorubicin-cyclophosphamide (AC) plus trastuzumab on page 941. Albanell et al. disclose that the biological reasons and clinical implications for the observed increase in cardiotoxicity with the combination of trastuzumab plus AC are currently being investigated.

Albanell et al. do not teach disclose or suggest the use of pegylated liposomal doxorubicin. Parahadadiopoulos et al. directed to PEG-liposomes (discussed above) do not teach, disclose or suggest the use of pegylated lipopsomal doxorubicin with trastuzumab (with or without another antineoplastic agent such as cyclophosphamide). Kastrup et al (mentioned above) discuss doxorubicin HCl.

There is no motivation in the references to combine the references in the manner necessary to arrive at Applicants' claimed invention. That is there is no motivation provided in the references to substitute the doxorubicin in Albanell et al. with Applicants' pegylated liposomal doxorubicin.

Support for the lack of motivation and lack of obviousness is found in the relative publication dates of the primary and secondary references. The primary reference, Albanell et al., has a 1999 publication date ("Drugs of Today 1999"). The secondary reference, Parahadadiopoulos et al., has a 1991 publication date (Proc. Natl. Acad. Sci USA, Vol. 88, pp. 11460-11464, December 1991). Thus, even though the secondary reference was available well before the primary reference, the primary reference does not utilize the information found in the secondary reference.

Applicants' claimed invention is deemed to patentably distinguish over the cited references.

The Examiner is requested to reconsider and withdraw this rejection.

Rejection under 35 U.S.C. 103(a)

Claims 1-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Albanell et al. and Kastrup et al. and Parahadadiopoulos et al., and further in view of Waksal et al. and the abstract of Hudis et al.

The cited references alone or combined do not teach, disclose or suggest Applicants' claimed invention.

The remarks above directed to to Albanell et al., Kastrup et al. and Parahadadiopoulos et al. apply equally as well here.

Waksal et al. disclose a method of inhibiting the growth of refractory tumors that are stimulated by a ligand of epidermal growth factor receptor (EGFR). The method comprises treating with an EGFR/HER1 antagonist and a chemotherapeutic agent. This reference has already been discussed above, and the remarks apply equally as well here.

Hudis et al. report that the feasibility and efficacy of sequential dose-dense therapy with doxorubicin, paclitaxel, and cyclophosphamide were studied in woman with breast cancer.

Hudis et al. do not suggest Applicants' claimed methods of treatment with pegylated liposomal doxorubicin, trastuzumab with or without another antineoplastic agent (such as cyclophosphamide).

Therefore, the addition of Waksal et al. and Hudis et al. does not remedy the deficiencies of Albanell et al. and Kastrup et al. and Parahadadiopoulos et al.

Applicants' claimed invention is deemed to patentably distinguish over the cited references.

The Examiner is requested to reconsider and withdraw this rejection.

Respectfully submitted,

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